REMARKS

After amendment, claims 4-6 and 14-20 are pending in the instant application. Claims 11-12 have been canceled in view of the restriction requirement. Applicants reserve the right to pursue the subject matter of the canceled claims in any continuing or related application. The amendment to claim 4 is fully supported by the specification as filed at page 14, lines 26-30.

New claims 14-20 are presented to particularly claim various aspects of the elected invention. No new matter is presented by these claims. Claim 14 is fully supported by the specification as filed at, for example, page 14. Support for claim 15 can be found in the examples at page 42-43, and at page 9, lines 32-36. The description supports new claim 16 at, for example, page 37, lines 22-32. New claims 17-19 are supported by the specification as filed at, *inter alia*, pages 38-41, and new claim 20 finds support at page 37.

I. The Restriction Requirement

The Examiner has restricted the claims of the instant application into Group I (claims 4-6) and Group II (claims 11-12) for examination purposes. Applicants hereby affirm the election, without traverse, of Group I.

II. The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 4-6 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, when the factors enumerated in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) are weighed, one skilled in the art could not practice the invention without undue experimentation. In particular, the Examiner notes that the methods of the invention are not taught by the prior art, although the art does teach effective treatment of certain diseases (such as cardiovascular disorders) with relaxin. The Examiner also concedes that the relative skill of those in the art is high. However, because of the factors relating to predictability or unpredictability of the art, breadth of claims, amount of direction or guidance and presence of working examples, and quantity of experimentation, the Examiner has rejected the claims. This rejection is traversed in part, and obviated in part by amendment.

A basis for the invention is Applicants' discovery of the biological activities of relaxin like factor. Specifically, Applicants synthetically produced relaxin like factor (for the first time) and showed it to have fairly high and specific affinity for a relaxin receptor on human cell membranes (specification at 36). Further, Applicants discovered that relaxin like factor provokes, in many cases, similar cellular responses as that caused by relaxin. For example, relaxin like factor had similar activity to relaxin in maintaining sperm motility when assayed in vitro (specification at 37). In other examples, relaxin like factor exhibited similar efficacy as relaxin in preventing deposition of extracellular matrix molecules by human fibroblast cells (specification at 40 et seq.), and in stimulating cAMP production by normal human endometrial cells (specification at 42). Moreover, Applicants made the surprising discovery that relaxin like factor acts *synergistically* with relaxin to promote softening of pubic ligaments in an *in vivo* mouse assay (specification at 42-43). Thus, Applicants have demonstrated by way of actual working examples, both *in vitro* and *in vivo*, the medically relevant uses of relaxin like factor.

The claims, as amended are directed to methods of using relaxin like factor to treat conditions susceptible to treatment with relaxin, as well as particular methods of using relaxin like factor to manipulate cellular responses. Particular diseases recited include cardiovascular disease, neurologic disease, sinus bradycardia, depression, hair loss, and diseases related to uncontrolled or abnormal collagen or fibronectin formation such as scleroderma. Each of these diseases has been shown to be susceptible to treatment with relaxin. The techniques used to administer relaxin to treat these diseases are well known to those of skill in the art, and Applicants also describe generally in the specification (at 13-25) how relaxin like factor can be administered in a similar manner. Applicants teach how to make relaxin like factor and specific truncated analogs, as well as a number of different assays that can be easily used by those of skill in the art to test the biological activity of relaxin like factor analogs. Applicants submit that, using the correct legal standard, the recited methods are fully enabled by the instant specification, and no undue experimentation is needed to practice the claimed invention.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue include: the amount of effort involved, *the*

guidance provided by the specification, the presence of working examples, the amount of pertinent literature, and the level of skill in the art. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the *art* can be considered in determining whether the required experimentation is undue, mere unpredictability of the *result* of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals cautioned that the unpredictability of the result of an experiment is *not* a basis to conclude that the amount of experimentation is undue. Specifically, the Court stated that:

> [If to fulfill the requirements of § 112, first paragraph, an Applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction* whether the claimed product will be obtained, . . . then *all* "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the Patent Act.

In re Angstadt, 190 USPQ 214, 219 (CCPA 1976) [emphasis in the original].

The claims, as amended, recite methods of using relaxin like factor and truncated derivatives that are therapeutically effective. Applicants teach that relaxin like factor may be used in a similar manner as relaxin to treat conditions susceptible to treatment with relaxin; methods of using relaxin to treat disease are well recognized in the art. The specification teaches that relaxin is homologous to relaxin like factor, that relaxin has a core domain that is sufficient for activity (*see e.g.*, specification at 10 and U.S. Patent 5,023,321) and describes similar peptide analogues of the relaxin like factor that should also be active. The specification also teaches a number of different assays for routinely testing the relaxin activity of these peptides: to maintain sperm motility (*see e.g.*, specification at 37); to inhibit expression of fibronectin *in vitro* (*see, e.g.*, specification at 41); to inhibit expression of collagen (*see, e.g.*, specification at 40); to increase expression of procollagenase (*see, e.g.*, specification at 41); to increase levels of cAMP produced by normal human endometrial cells grown *in vitro* (*see, e.g.*, specification at 42); and to relax the pubic ligament *in vivo* in a mouse model system (*see, e.g.*, 42-43). Thus, the disclosure teaches the skilled artisan how to determine by *routine* experimentation suitable peptides for use as presently claimed.

Applicants respectfully submit that due to the guidance in the specification for routine efforts in producing and testing the compounds, the presence of specific working examples, and the high level of skill in the arts of biochemistry and medicine, one of ordinary skill in the art would be able to make and use the entire scope of the claimed invention without undue experimentation. Below, Applicants address and rebut each point raised by the Examiner in support of the rejection.

A. Predictability or Unpredictability

With respect to predictability, the Examiner asserts that the significance of particular amino acids cannot be predicted a priori but must be determined by "painstaking experimental study" (Office Action, page 3), and cites the reference by Rudinger for support. Additionally, the Examiner cites Yuen for examples of previous attempts to treat nervous system degenerative diseases with peptides. The Examiner asserts that although initial experimentation with neurotrophic factors such as CNTF, BDNF and NGF to treat neurological disorders was encouraging, clinical trials demonstrated the factors to be ineffective due to side-effects. Applicants respectfully traverse.

The Examiner's reliance on Rudinger is misplaced. Applicants submit that even if "painstaking experimental study" was the standard for "undue experimentation" (which it is not), Rudinger does not support non-enablement of the claims. Applicants are not claiming the use of every peptide of any sequence that has relaxin activity- the claims recite a particular peptide, relaxin like factor, and particular truncations of this peptide. Applicants have actually shown by *in vitro* studies and an *in vivo* study the biological effectiveness of relaxin like factor. As discussed above, the specification describes in detail any number of different assays, assays that can be routinely practiced by those of only ordinary skill, for determining the activity of different relaxin like factor analogues. Further, the Examiner's reliance on Yuen in support of the allegation that the properties of a peptide in an *in vitro* system do not necessarily correlate to *in vivo* success is also misplaced. Applicants submit that merely because some therapies, after extensive clinical trials, are found to have side effects that are intolerable with commercialization of the therapy cannot be automatically extended to all therapies. Applicants note, however, that Yuen also describes the results with IGF-I as promising, thus negating a sweeping generalization against the success of any type of peptide treatments that can be drawn from Yuen.

With regard to the Examiner's allegation that the extrapolation of *in vitro* studies is unpredictable, Applicants submit that the value of *in vitro* studies(and animal studies as described in the specification) in extending knowledge of a pharmaceutical agent's activities in humans is well documented. *In vitro* studies provide basic biochemical information about cellular responses to an peptide. Animal studies provide crucial information about possible interactions between a drug and tissues and organs, as well as to its likely effects on cardiovascular, respiratory, central nervous systems, etc. These studies assist us in determining whether it is safe to proceed to clinical studies in humans as well as dosages that may be safely employed. It has never been the practice of the PTO, or the Courts, to require that actual human clinical studies (which require substantial expenditures of money and time) be conducted to support enablement of claims to methods of treatment. Yet, this is precisely the standard that the Examiner would have us adopt by rejecting Applicants' *in vitro* results and *in vivo* animal study.

The Examiner's stated concerns regarding the alleged unpredictability of the effect of relaxin like factor activity in humans clearly relate to the Examiner's doubts as to whether the present invention will operate as described in the specification. This is indeed a utility rejection under § 112. Applicants contend that the Utility Guidelines are applicable to this rejection (Utility Guidelines 60 F.R. 36263, Legal Analysis, I.D.; M.P.E.P. § 2107(d); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)). The Utility Guidelines state that the standard for imposing a lack of utility rejection under § 101 and § 112 is the same, and therefore, "Office personnel should not impose a § 112, first paragraph, rejection grounded on 'lack of utility basis' unless a § 101 rejection is proper". Thus, a utility rejection which is not proper under § 101 cannot be made under § 112. (Utility Guidelines 60 F.R. 36263, Legal Analysis, I.D.; M.P.E.P. § 2107(d))

Under the Utility Guidelines, evidence of utility is sufficient if it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (Utility Guidelines 60 F.R. 36263, Legal Analysis, II.G.; M.P.E.P. § 2107.01(f)). <u>If reasonably correlated to a particular pharmaceutical utility, data generated using *in vitro* assays, or from testing in an animal model, or a combination of both, almost invariably will be sufficient to establish the asserted utility</u>. Lack of an appropriate animal model to assess effectiveness of a treatment modality prior to the filing date should not itself preclude a finding that an invention has utility. There is no requirement to provide data from human

clinical trials for establishing utility of an invention related to treatment of human disease. All that is required is a reasonable correlation between the effectiveness of the methods and the asserted use. (*See* Utility Guidelines, 60 F.R. 36263, Legal Analysis, III, Sections A-F; M.P.E.P. § 2107.02, Sections a-f).

These principles were, in fact, applied by the Court of Appeals for the Federal Circuit (CAFC) in its reversal of the Patent Office's rejections under § 112 in *In re Brana*. In its decision, the CAFC stated the following legal standard for compliance with the § 112 utility requirement: "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support," a specification's disclosure "must be taken as in compliance with the enabling requirement." Id. at 1441 (emphasis in the original).

The CAFC pointed out in *In re Brana* that the testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug or therapeutic method for public use. *Id.* at 1442. More specifically, the CAFC explained the following standard for determining the utility of a pharmaceutical composition under 35 U.S.C. § 112:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas... (*Id.* at pp. 1442-1443).

In the present case, the specification provides experimental data which demonstrate that peptides used according to the claimed methods are effective in: maintaining sperm motility; inhibiting collagen production *in vitro*; inhibiting fibronectin production *in vitro*; activating expression of procollagenase; and pubic ligament softening in mice. Applicants submit that the disclosure of the specification provides a reasonable correlation between the effectiveness of the peptides utilized according to the claimed methods and the use of these methods to treat a medical condition that is ameliorated by treatment with relaxin. Accordingly, Applicants submit that the disclosure is sufficient to establish utility.

In summary, the P.T.O. Utility Guidelines and the CAFC (in *In re Brana*) clearly state that if a utility rejection is improper under § 101, a utility rejection cannot be made under § 112. In the present case, the utility of the claimed methods is demonstrated by evidence presented in the specification. Accordingly, under the standard set forth in the Utility Guidelines and in *In re Brana*, the claimed methods meet the utility requirements of § 112 and are fully enabled.

For all the above reasons, Applicants respectfully submit that the rejection of claims 4-6 under 35 U.S.C. § 112, first paragraph, has been overcome and request that the rejection be reconsidered and withdrawn.

B. Breadth of claims

With respect to the breadth of the claims, the Examiner asserts that the claims do not clearly specify in what manner how many of the disorders are treated. As an example, the Examiner asks how are neurodegenerative disorders treated, does treatment involve regeneration of cells or an improvement in motor skills. Applicants submit that claim 4, as amended, obviates this rejection. Claim 4 has been amended to clarify that the condition is ameliorated or prevented by the administration of the relaxin like factor. Applicants submit that any type of amelioration of a symptom is art-recognized as treatment, and the patent laws do not require an applicant to detail the precise mechanisms of his invention. Therefore, withdrawal of the rejection on this basis is respectfully requested.

C. Amount of Direction or Guidance and Working Examples

As for the factors relating to amount of direction and working examples presented, the Examiner comments that ample guidance is not presented in the specification as to the manner in which each disorder is to be treated and that there are no working examples of treating diseases. The Examiner asserts that guidance is necessary since for some diseases, known compounds have proven *ineffective*.

Additionally, the Examiner again cites Rudinger, this time for the proposition that the effect of truncations in amino acids cannot be predicted but must be tested by "painstaking experimental study." Further, the Examiner states:

> . . . in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required [citations omitted]. *In re Dreshfield* [citation omitted] gives this general rule: "It is well settled that in

cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

The Examiner also states that "the specification is void of any examples demonstrating that truncation of the peptide does not alter the activity of the peptides and *thus are still useful in treating the claimed disorders*." Office Action at page 5.

As noted above, the requirements of § 112 do not demand that Applicants to obtain positive Phase II clinical results in order to enable claims to methods of treatment- the *in vitro* and animal models of activity presented by Applicants suffice to establish the utility of the claimed methods. Applicants have addressed the Rudinger reference above. With respect to the amount of guidance, Applicants submit that not only have they provided guidance in how to use the relaxin like factors of the invention to treat diseases (*see e.g.*, specification at 13-25), but that methods of using relaxin to treat diseases are exceedingly well know to those of skill in the art. For example, relaxin is has been administered to patients in Phase II clinical trials, and shown a statistically significant improvement in skin score, the primary clinical endpoint (*see e.g.*, www.connetics.com/relaxin, copy attached). Thus, those of skill in the art would know how to use not only relaxin, but also relaxin like factor, to treat scleroderma or any other disease for which relaxin treatment is effective.

Moreover, the Examiner's stated concern that truncations may not still be "*useful in treating the claimed disorders*" appears to be a rejection based upon utility. Applicants have discussed the error in this aspect of the rejection above. However, in order to clarify that Applicants are not claiming truncations of relaxin like factor that are biologically inactive, Claim 4 has been amended to recite that the recited method results in amelioration or prevention of the disorder or condition. It is well settled in law that one can draft a claim with a functional limitation so as to exclude those embodiments that do not provide a desired benefit (*e.g.*, altering activity). *In re Halleck*, 422 F.2d 911, 164 U.S.P.Q. 647 (CCPA 1970), *In re Boller*, 332 F.2d 382, 141 U.S.P.Q. 740 (CCPA 1964), *In re Fuetterer*, 319 F.2d 259, 138 U.S.P.Q. 217 (CCPA 1963). Using the *in vitro* and *in vivo* assays described in the specification, it would take no undue experimentation to determine those truncations of relaxin like factor that have relaxin activity.

D. Quantity of Experimentation

The Examiner states that the claims encompass many different diseases, and asserts at page 5 that:

> one of ordinary skill would be burdened with undo experimentation to determine to what disorders the relaxin like polypeptide would be most effective in and condition to treat. Even for the specific disorders claimed one still would be burdened with undue experimentation to determine in what manner the condition[s] is to be treated. Moreover, the claims also allow for the use of truncated peptides of Relaxin like Polypeptides . . . .

Applicants acknowledge that conditions susceptible to treatment with relaxin are associated with a diverse array of medical conditions. However, Applicants point out that this association is the result of a common biological response; the response to relaxin. Accordingly, since the relaxin like peptides of the invention have similar biological activities as relaxin, and indeed in some situations are synergistic with relaxin, one skilled in the art would reasonably expect that if the administration of a relaxin treats one medical condition, relaxin like factor would also be effective in treating that condition. One of skill need only look to those diseases found susceptible to treatment with relaxin for use in the methods of the invention.

Further, in accord with *In re Angstadt*, Applicants submit that the relevant inquiry is not whether the specification enables one skilled in the art to predict whether a condition susceptible to treatment with relaxin could also be treated with relaxin like factor, but rather whether the experimentation needed to test the ability of a method to treat a condition susceptible to treatment with relaxin could also be treated with relaxin like factor is undue, *i.e.*, would require ingenuity beyond that to be expected from one of ordinary skill in the art. Clearly, only routine procedures are required to test the relaxin like factor polypeptides taught by the specification and used according to the claimed methods to treat a medical susceptible to treatment with relaxin.

As above, Applicants submit that, it has never been the practice of the PTO, or the Courts, to require that actual human clinical studies be conducted to support enablement of claims to methods of treatment. Moreover, applicants point out that in *In re Brana*, the CAFC deemed that test results showing *in vivo* antitumor activity of compounds against a standard tumor model in mouse is acceptable as evidence of utility sufficient to meet the requirement of 35 U.S.C. § 112, first paragraph.

The Applicants assert that the foregoing amendment and remarks overcome or obviate the rejections under 35 U.S.C. § 112, first paragraph. Accordingly, the rejections should be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. In view of the above amendments and comments, it is believed that the Examiner's rejection of the claims under 35 U.S.C. § 112 first paragraph has been obviated and that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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